UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/651,290	08/30/2000	Marcin S. Filutowicz	P00154US/13238/00016	2591

7590 07/12/2002

Janet E Reed
Saul Ewing Remick & Saul LLP
Centre Square West
1500 Market St 38th Floor
Philadelphia, PA 19102

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 07/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/651,290	Applicant(s) FILUTOWICZ, MARCIN S.
	Examiner Vanessa L. Ford	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *27 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,16-27 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14, 16-17 and 29* is/are rejected.

7)☒ Claim(s) *18-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Office Action is responsive to Applicant's response filed February 27, 2002 is acknowledged. Claims 15 and 30 have been cancelled. Claims 1, 14 and 29 have been amended.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

REJECTIONS WITHDRAWN

3. In view of Applicant's amendment the following Rejections have been withdrawn:

a) Rejection of claims 14-15 under 35 U.S.C. 112, second paragraph, pages 6-7, paragraph 3 of previous Office action.
b) Rejection of claims 15-24, 31-32 and 41 under U.S.C. 102(b), pages 7-8, paragraph 4 of the previous Office action.
c) Rejection of claims 57-59 under 35 U.S.C. 102(b), pages 9-10, paragraph 5 of the previous Office action.

CLAIM OBJECTIONS

4. Claims 18-27 are objected to because they depend from rejected based claims.

REJECTIONS MAINTAINED

5. The rejection of claims 1-12, 14, 16-17 and 29 are rejected under 35 U.S.C. 112, first paragraph is maintained for the reason set forth on pages 2-6 of the previous Office Action.

The rejection was on the grounds that the specification contained subject matter which was not described in the in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and optionally, at least one screenable marker gene and a pharmaceutical preparation comprising the antibacterial agent.

The specification generically claims an antibacterial agent that comprises a non-pathogenic donor bacterial cell harboring at least one transmissible plasmid comprising an origin of replication, an origin of transfer and optionally at least one screenable gene marker. The claimed invention further includes a plurality of microorganisms of which the donor cell or recipient cell can be obtained. The specification does not provide substantive evidence that the claimed antibacterial agent can maintain stability or that the pharmaceutical preparation comprising the antibacterial agent is capable of treating bacterial infections. This demonstration is required for the skilled artisan to be able to use the claimed invention for the intended purpose of treating bacterial infections. Without this demonstration, the skilled artisan would not be able to reasonably predict whether the claimed invention could survive *in vivo* use or whether the artisan would be able to predict if the administration of the claimed pharmaceutical preparation, would be able to treat bacterial infections.

There are several factors that contribute to the stability of plasmids that are well known in the art. These factors include: 1) the ability of conjugative transfer within and between genera, 2) essential components required to ensure stabilization 3) mating pair stabilization and 4) compatibility between the donor and recipient cell. The ability to reasonably predict the capacity of plasmids to be conjugatively transferred within genera and especially between genera, maintain stability is problematic. This is evidenced by Ambrozic et al, *Microbiology (ENGLAND), February 1998, 144(Pt 2), p. 343-352).* Ambrozic et al teach that conjugal transfer was demonstrated with low frequency to *Klebsiella pneumoniae* suggesting that a natural barrier effectively bars transfer. Specific sequences are also required for the complete stabilization of plasmids. For example, Roberts et al, *(Journal of Bacteriology, November 1990, 172 (11), p. 6204-6216)* teach that one of the regions responsible for stable inheritance of the broad host range plasmid RK2 is contained within the PstI C fragments. Robert et

al teach that the PSTI C fragment itself is not required for stabilization activity, however the PSTI C fragment encodes a multimer resolution system which required adjacent sequence to maintain complete stabilization. Mating stabilization during conjugative transfer between the donor and recipient cell is also required. Klimke et al, *(Journal of Bacteriology, August 1998, 180 (16), p. 4036-4043)* teach that mating stabilization occurs during conjugative transfer whereby the donor cell and recipient cells form a tight junction which requires pili as well as TraN and TraG (proteins involved in matting pair stabilization) in the donor cell. Klimke et al teach that the TraN and not the F pili appears to interact with OmpA and LPS moieties during conjugation, resulting in mating stabilization. Klimke et al further teach that this is the first step in efficient mobilization of DNA. Compatibility between the donor cell and the recipient cell is also necessary. This is further evidenced by Rahal et al, *(Annales de microbiologie (FRANCE), May-June 1978, 129 (4), p. 409-414)*. Rahal et al teach that very few multi-resistant strains of *Vibrio cholerae* have been isolated this may be due to a high frequency of plasmids being lost due to the incompatibility of groups. Since genetic mutations are used to determine the structural and functional properties of the claimed antibacterial agent and pharmaceutical composition the predictability of which changes or mutations can be tolerated in the host and still retain similar activity requires a knowledge of and guidance with regard to which mutations can be made in the plasmid wherein stability will be maintained. The cited references have shown that unpredictability exists regarding plasmid stability. Therefore, it can be concluded that undue experimentation would be required to make and use the claimed antibacterial agent without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the pharmaceutical preparation commensurate in scope with these claims. The specification fails to teach how to make and use the claimed pharmaceutical preparation. The term "pharmaceutical" encompasses the ability of the specific antigen to induce protective immunity to a host. The specification does not disclose how to formulate the pharmaceutical preparation or what dosages are required to treat a patient with a bacterial infection? The specification further does not disclose whether the antibacterial agent can be survive the mouth, stomach or intestines without being degraded or if the antibacterial agent is capable of reach the target organs necessary to treat a particular bacterial infection. Therefore, it is unclear as to how to formulate a pharmaceutical preparation comprising the antibacterial agent which will treat **any** bacterial infection.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or

guidance is presented in the specification with respect to selecting a stable antibacterial agent and pharmaceutical preparation that would achieve a desire level of success when administered to a patient with a bacterial infection that is capable of treating that bacterial infection, 3) there are limited working examples which suggest the desired results of a antibacterial agent that is to be used in a pharmaceutical preparation to treat any bacterial infection, 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

Applicant urges that the present application teaches antibacterial agents comprising "killer plasmids" which are conjugatively transferred from a nonpathogenic donor to a pathogenic recipient and the application teaches that both *ori* and *tra* are required. Applicant urges that the instant disclosure has clearly and precisely pointed out the limitations of what he regards as his invention. Applicant urges that the Examiner is reading into the claims a limitation that is not contained within the invention. Applicant urges that he considers the stability of the plasmid in neither the donor nor the recipient to be critical to the operation of the invention as claimed and that the more important parameter is that the bacteria are capable of conjugatively transferring the plasmid to a recipient cell. Applicant urges that there is no limitation within the claimed in invention regarding *in vivo* survival or use. Applicant urges that Ambozic et al supports the proposition that a "natural barrier " effectively bars transfer of a plasmid by conjugal transfer to *Klebsiella pnuemoniae*. Applicant also urges that the claimed invention differs because it teaches wide host range plasmids and that Ambozic et al only teach the use of narrow host range plasmids (i.e. ColV). Applicant urges that any toxic or killing effect of the plasmid would not be present until after the successful

conjugative transfer to the recipient and that *Klebsiella* is not specifically claimed. Applicant urges that Roberts et al support the position that specific sequences are required for complete stabilization of plasmids. Applicant urges that without complete stabilization a loss of even 10 to 12% would not render the invention inoperable or unable to be practiced. Applicant urges that Klimke et al teach that mating stabilization during conjugative transfer between donor and recipient cell is required. Applicant urges that in order to practice the claimed invention transfer genes would have to be present. Applicant urges that Rahal et al disclose that compatibility between donor cell and the recipient cell is necessary. Applicant urges that the finding disclosed by Rahal et al do not preclude one from practicing the claimed invention.

Applicant's arguments filed February 27, 2002 have been fully considered but they are not persuasive. The claims are drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication, an origin of transfer and optionally, at least one screenable marker gene wherein the donor cell further comprises one or more transfer genes conferring upon the donor cell the ability to conjugatively transfer the transmissible plasmid to the recipient cell and wherein the donor cell produces the plasmid replication repressor and further wherein at least one recipient cell is a pathogenic bacterium that does not produce the plasmid replication repressor, thereby enabling the transmissible plasmid to undergo runaway replication in the recipient cell. Despite the knowledge in the art for using antibacterial agents, the specification fails to specifically point out how to make and use the claimed invention. Applicant asserts that

the Examiner is reading limitations that are not included in the claimed invention. The Examiner points out that the Applicant must provide in the instant specification information so that one skilled in the art could make and use the claimed invention. The specification fails to provide guidance regarding whether the experiments disclosed on pages 17-18 were done *in vivo* or *in vitro*? The specification discloses in Example 2 a mutated *pir* gene. Which mutation was used in Example 2? What mutations can be made in the antibacterial agent and the pharmaceutical composition can maintain its antibacterial activity? What pathogenic bacterial cells were killed? How would one monitor the killing of pathogenic cells *in vitro*? The specification states that "pharmaceutical preparations comprising the donor bacteria are formulated in dosage unit from for ease of administration and uniformity". The specification states "that the dosage unit form refers to a physically discrete unit of the pharmaceutical preparation appropriate for the undergoing of treatment" (page 16). Where patients treated with the pharmaceutical composition? What bacterial diseases where treated? Can any bacterial infection or disease be treated using the pharmaceutical composition? What concentration of the pharmaceutical composition is sufficient to treat a bacterial infection? Was the pharmaceutical composition able to reach the site of infection? The metes and bounds of the claimed invention cannot be ascertained by the information disclosed in the specification. Therefore, one of skill in the art would require guidance, in order to make and use the claimed invention. Without proper guidance, the experimentation is undue.

Applicant urges that Ambozic et al supports the proposition that a "natural barrier " effectively bars transfer of a plasmid by conjugal transfer to *Klebsiella pnuemoniae* and that the claimed invention differs because the claimed invention teaches wide host range plasmids and Ambozic et al teach the narrow host range plasmids (i.e. ColV). Applicant's claimed invention is drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication, an origin of transfer and optionally, at least one screenable marker gene wherein the donor cell further comprises one or more transfer genes conferring upon the donor cell the ability to conjugatively transfer the transmissible plasmid to the recipient cell wherein the result is runaway replication in the recipient cell. The claimed invention encompasses bacteria of the genera *Klebsiella.* The ability to reasonably predict the capacity of plasmids to be conjugatively transferred within genera and especially between genera, maintain stability is problematic. This is evidenced by Ambrozic et al. Ambrozic et al teach that conjugal transfer was demonstrated with low frequency to *Klebsiella pneumoniae* suggesting that a natural barrier effectively bars transfer. Applicant urges that any toxic or killing effect of the plasmid would not be present until after the successful conjugative transfer to the recipient and that *Klebsiella* is not specifically claimed. The claimed invention requires the transfer of a "transmissible plasmid" from a donor cell to a recipient cell. A toxic or killing effect cannot occur if the transmissible plasmid" is not conjugatively transferred from the donor cell to the recipient cell. Therefore, in view of the teaching of Ambrozic et al one can

reasonably assume that the capacity of plasmids to be conjugatively transferred within and between all genera of bacteria is unpredictable.

Applicant urges that Roberts et al support the position that specific sequences are required for complete stabilization of plasmids. Applicant urges that without complete stabilization a loss of even 10 to 12% would not render he invention inoperable or unable to be practiced. Roberts et al teach that one of the most important survival characteristics of naturally occurring plasmids the ability to ensure that both progeny of a cell division contain at least one copy of the plasmid and this often accomplished in spite of a very low number of plasmid copies per cell. Roberts et al teach that the replication control mechanism to ensure a constant number of plasmid copies per chromosome which provides a pool of plasmids for segregation to each daughter cell is crucial. Therefore, one skill in the art can reasonable assume that stabilization is necessary for conjugative transfer of a "transmissible plasmid" from a donor cell to a recipient cell wherein the result is runaway replication in the recipient cell.

Applicant urges that Klimke et al teach that mating stabilization during conjugative transfer between donor and recipient cell is required and that transfer genes would have to be present to practice the claimed invention. Since the claimed invention is directed to any bacterial donor and any recipient cell, the Klimke et al reference was cited to point out that mating stabilization during conjugative transfer between donor and recipient cell is required.

Applicant urges that Rahal et al disclose that compatibility between donor cell and the recipient cell is necessary. Applicant urges that the finding disclosed by Rahal et al do not preclude one from practicing the claimed invention. Rahal et al teach that very few multi-resistant strains of *Vibrio cholerae* have been isolated this may be due to a high frequency of plasmids being lost due to the incompatibility of groups. Since genetic mutations are used to determine the structural and functional properties of the claimed antibacterial agent and pharmaceutical composition the predictability of which changes or mutations can be tolerated in the host and still retain similar activity requires a knowledge of and guidance with regard to which mutations can be made in the plasmid wherein stability will be maintained. The cited references have shown that unpredictability exists regarding plasmid stability. Therefore, it can be concluded that undue experimentation would be required to make and use the claimed antibacterial agent without proper guidance.

The specification has also failed to provide guidance regarding how to use the pharmaceutical composition comprising the antibacterial agent. The specification does not specifically disclose whether the experiments disclose in Examples 1 and 2 were performed *in vivo* or *in vitro*, if all bacterial infections or diseases can be treated, if any concentration of the pharmaceutical is sufficient to treat a bacterial infection, if all mutations can be made in the antibacterial agent and the pharmaceutical composition is able to retain its antibacterial ability or if all pharmaceutical composition formulations are able to reach the site of infection? The metes and bounds of the claimed invention cannot be ascertained by the information disclosed in the specification. Therefore, in

view of the teaching of the cited prior art, one of skill in the art would require guidance, in order to use the claimed invention. Without proper guidance, experimentation is undue.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
June 3, 2002

MARK NAVARRO
PRIMARY EXAMINER